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A thermoreversible supramolecular hydrogel inspired by poly(*N*,*N*-dimethylacrylamide)

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A thermoreversible supramolecular hydrogel based on a silver(I) alkanethiolate bearing terminal *N*,*N*-dimethylamide groups has been prepared, which is inspired by poly(*N*,*N*-dimethylacrylamide). This demonstrates the possibility of designing supramolecular hydrogels inspired by conventional polymers, through the self-assembly of the corresponding mercapto-modified monomers promoted by the addition of a Ag^I salt.

Keywords: supramolecular hydrogels; self-assembly; silver; thiolates

The ability to form hydrogels is not limited to polymers. There are also some small molecules that self-assemble into a 3D network of fibres. These fibres form a gel in which the gelator molecules are solely held together by non-covalent interactions. These are known as supramolecular hydrogels or low molecular weight hydrogels (*1*), and are emerging as an alternative to conventional polymer-based hydrogels. Recently, the use of metal–ligand interactions has been shown to be a viable method for the construction of the so-called metallogels or metallo-supramolecular gels (*2*), although the method has been fundamentally used for the fabrication of organogels rather than hydrogels.

In a previous work, we demonstrated that a supramolecular hydrogel can be formed through the self-assembly of coinage metal glutathione thiolates (*3*). Here, we show that the method is not limited to the use of glutathione, by demonstrating that supramolecular hydrogels can also be obtained by using smaller hydrophilic thiols.

The aim of the present work was to study the following hypothesis: is it possible to create a supramolecular analogue of a conventional polymer through the self-assembly of a structurally similar monomer? If so, would this analogue then present similar gelling properties?

It is well known that several chemically cross-linked polymers and copolymers of *N*-alkyl substituted acrylamides form temperature-sensitive hydrogels and their use in biomedical applications is extensive (*4*). These polymers can be synthesised from the corresponding *N*-alkylacrylamide monomers by anionic or free-radical polymerisation using the appropriate initiator (*5*). Here, the hydrophilic amide groups are covalently bound to the polymer backbone. Thus, inspired by poly(*N*,*N*-dimethylacrylamide) (**2**), a thiol group was attached to the acrylamide monomer **1** (Scheme 1) to give amide **3**. The addition of $AgNO_3$ to **3** in water results in the formation of the corresponding thiolate, with a molecular formula of $Ag{-}S{-}CH_2CH_2CON(CH_3)_2$ (Equation (1)). This compound self-assembles into the supramolecular polymer **4** that subsequently gives a hydrogel. This species consists of a Ag—S backbone from which *N*,*N*-dimethylamide groups are appended perpendicularly (*6*).

$$n\mathrm{HS}{-}\mathrm{CH_2CH_2CON(CH_3)_2} + n\mathrm{AgNO_3} \rightarrow [\mathrm{Ag}{-}\mathrm{S}{-}\mathrm{CH_2CH_2CON(CH_3)_2}]_n + n\mathrm{HNO_3}. \quad (1)$$

The material was freeze-dried and analysed by IR spectrophotometry. The main feature of this spectrum is the absence of the S—H stretching band, which appears at 2539 cm^{-1} for **3** (see Supplementary Material online). Energy dispersive X-ray spectroscopy semiquantitative elemental analysis was consistent with a $Ag{-}S{-}CH_2CH_2CON(CH_3)_2$ molecular formula, showing a 1:1 sulphur/silver ratio.

Thiolate **4** is able to form a gel at concentrations as low as 0.5% (w/v) and the resulting hydrogel is stable for several months at room temperature. The gel shows a thermoresponsive behaviour, which is typical for supramolecular hydrogels (*1*). When heated above the gel melting temperature (T_{gel}), the system behaves as a clear solution and a gel is formed again when allowed to cool (Scheme 2). The thermal stability of the hydrogel at different gelator concentrations (0.5–2%, w/v) was studied. Figure 1 shows that within this concentration range, the T_{gel} of the

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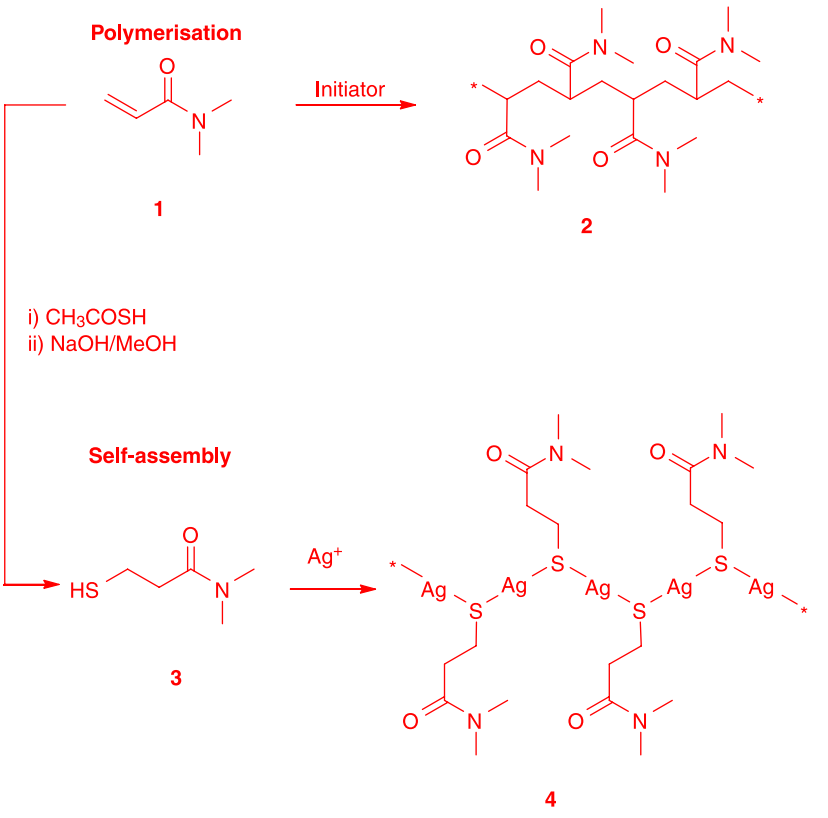
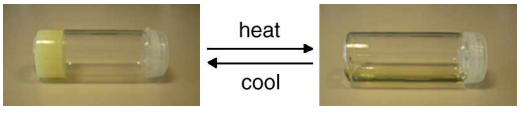


Scheme 1. Structural analogy of poly(*N*,*N*-dimethylacrylamide) **2** prepared from *N*,*N*-dimethylacrylamide **1**, and self-assembled thiolate **4** prepared from *N*,*N*-dimethyl-3-mercaptopropanamide **3** and $AgNO_3$.

supramolecular hydrogel is well expressed by a linear function of the thiolate concentration. Thus, T_{gel} was found to increase with the temperature, in concurrence with the literature for other supramolecular hydrogels (*7*).

SEM analysis of the freeze-dried hydrogel reveals a porous 3D network in form of fibres (Figure 2(a)). TEM shows that the fibres themselves are composed of a granular pattern rather than being continuous (Figure 2(b),(c)) (*8*). A close-up view of an individual fibre (Figure 2(d)) reveals that the pattern consists of dark-contrasted and irregular-shaped granules adhered by an uncontrasted (soft matter) matrix. The granules are about 3.5–5 nm in diameter, and would correspond to oligomeric species of **4**. The width of the soft matrix is generally found to be at least 0.6 nm in size and can often reach up to 1.5 nm, but rarely above. Taking into account that the matrix is not contrasted in the TEM and that its width matches at least the size of amide **3** while usually staying within the length of two elongated molecules, it is assumed that the amide chains act as the glue for the aggregation of the oligomeric silver thiolate granules through van der Waals and hydrophobic forces. Thus, the phase transition of the hydrogel when heated above T_{gel} is thought to occur as a result of the disaggregation of these



Scheme 2. Thermoreversible sol/gel transition of hydrogel **4** (1%, w/v).

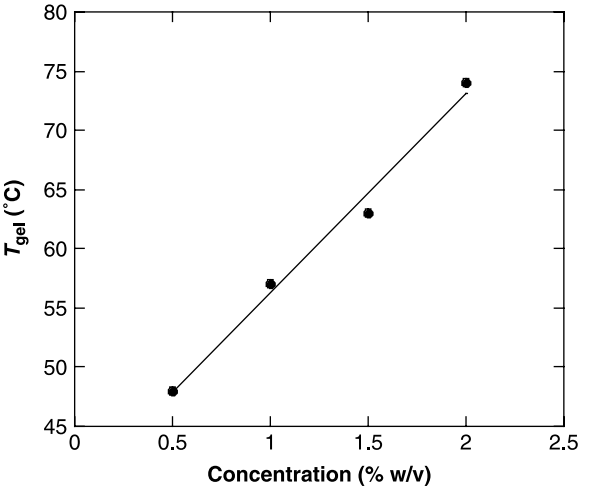


Figure 1. Variation of T_{gel} with the concentration of hydrogelator **4**.

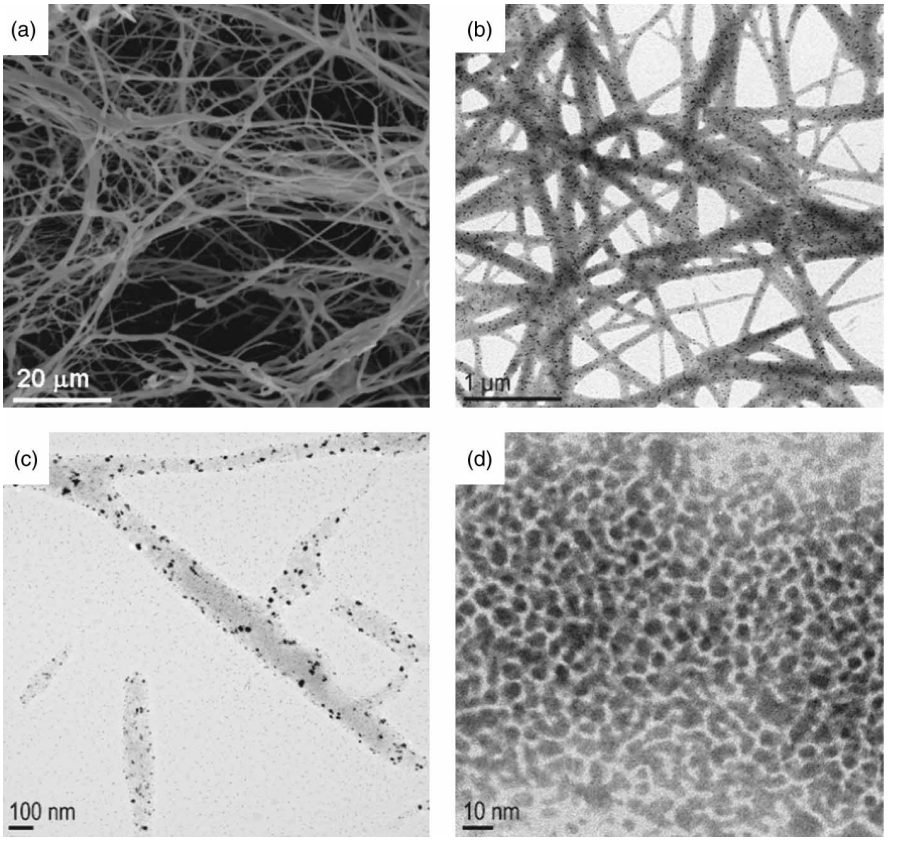


Figure 2. SEM (a) and TEM (b), (c) and (d) micrographs of the freeze-dried hydrogel.

oligomeric granules, which are then stable and soluble in water. However, further investigation will be needed in order to fully understand the detailed structure of this oligomeric system and the interactions between the amide chains that take part in this thermoreversible process.

In conclusion, a mercapto-modified acrylamide monomer has been used for the fabrication of a supramolecular polymer that forms a thermoreversible hydrogel. This demonstrates the possibility of designing supramolecular hydrogels, inspired by conventional polymers, through the self-assembly of the corresponding mercapto-modified monomers promoted by the addition of a Ag^I salt. The fact that the self-assembly occurs after the addition of the second component (*9*) makes the system ideal for applications that require *in situ* gel formation (*10*).

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